

FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (REV. 1094)		ATTORNEY'S DOCKET NUMBER K0448/7003
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		<b>09/673341</b> U.S. APPLICATION NO. (If known, see 37 CFR 1.77)
INTERNATIONAL APPLICATION NO. PCT/JP99/01868	INTERNATIONAL FILING DATE 08 April 1999 (08.04.99)	PRIORITY DATE CLAIMED 17 April 1998 (17.04.98)
TITLE OF INVENTION ADHESIVE PREPARATIONS		
APPLICANT(S) FOR DO/EO/US KURITA, Hisakazu, TATEISHI, Tetsuro, CHONO, Hideharu, HIGO, Naruhito		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
<ol style="list-style-type: none"> <li>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>3. <input checked="" type="checkbox"/> This express request to begin national procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).</li> <li>4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.</li> <li>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)).             <ol style="list-style-type: none"> <li>a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).</li> <li>b. <input type="checkbox"/> has been transmitted by the International Bureau.</li> <li>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ol> </li> <li>6. <input checked="" type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)) with verification of translation.</li> <li>7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).             <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).</li> <li>b. <input type="checkbox"/> have been transmitted by the International Bureau.</li> <li>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li>d. <input checked="" type="checkbox"/> have not been made and will not be made.</li> </ol> </li> <li>8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</li> <li>9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371§(4)).</li> <li>10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(C)(5)).</li> </ol>		
<b>Items 11. To 16. Below concern document(s) or information included:</b> <ol style="list-style-type: none"> <li>11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98 with references.</li> <li>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</li> <li>13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment.              <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</li> <li>14. <input type="checkbox"/> A substitute specification (submitted as a first Preliminary Amendment).</li> <li>15. <input type="checkbox"/> A change of power of attorney and/or address letter.</li> <li>16. <input checked="" type="checkbox"/> Other items or information:              Copy of PCT Written Opinion with a sworn English translation              Copy of Response to Written Opinion with a sworn English translation              Copy of PCT International Preliminary Examination Report w/a sworn English translation              Copy of PCT Published Application w/international Search Report and English translation of Search Report              Copy of PCT/IB/301, 304, 306, 308, and 332</li> </ol>		
Express Mail Label No. EL682257191US Mailed October 13, 2000		

U.S. APPLICATION NO. (If known, see 37 CFR 1.51)		INTERNATIONAL APPLICATION PCT/JP99/01868	ATTORNEY'S DOCKET NUMBER K0448/7003
17. X The following fees are submitted:		CALCULATIONS <small>PTO USE ONLY</small>	
<b>BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):</b>			
Search Report has been prepared by the EPO or JPO .....		\$860.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) .....		\$690.00	
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))..		\$710.00	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....		\$1000.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)		\$100.00	
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>		\$860.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 X 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total Claims	12-20 =	0	X \$18.00
Independent Claims	1 - 3 =	0	X \$78.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)		+\$270.00	
<b>TOTAL OF ABOVE CALCULATIONS =</b>		\$860.00	
Reduction by $\frac{1}{2}$ for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).		\$	
<b>SUBTOTAL =</b>		\$860.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).		\$	
<b>TOTAL NATIONAL FEE =</b>		\$860.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate coversheet (37 CFR 3.28, 3.31). \$40.00 per property +		\$0.00	
<b>TOTAL FEES ENCLOSED =</b>		\$860.00	
		Amount to be: refunded	\$
		charged	\$
<p>a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>860.00</u> to cover the above fees is enclosed.</p> <p>b. Please charge by Deposit Account No. _____ In the amount of \$ _____ To cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23/2825. A duplicate of this sheet is enclosed.</p>			
<p><b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b></p>			
SEND ALL CORRESPONDENCE TO		 <small>SIGNATURE</small>	
John R. Van Amsterdam WOLF, GREENFIELD & SACKS, P.C. 600 Atlantic Avenue Boston, Massachusetts 02210		<u>John R. Van Amsterdam</u> NAME	
		40,212 REGISTRATION NO	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: KURITA et al.  
Int'l Application No.: PCT/JP99/01868  
Int'l Filing Date : April 8, 1999  
U.S. Serial No: Unknown  
Filed: Herewith  
For: ADHESIVE PREPARATIONS

Box PCT  
COMMISSIONER FOR PATENTS  
WASHINGTON, D.C. 20231

Sir:

**PRELIMINARY AMENDMENT**

Please amend the application as follows, prior to calculation of the fees.

**In the Claims**

Please amend the claims as follows:

3. (amended) The adhesive preparation according to claim 1 [or 2] comprising the organic acid salt of 0.01-15% by weight.

4. (amended) The adhesive preparation according to claim 1 [or 2] comprising the base drug salt of 0.1-20% by weight.

5. (amended) The adhesive preparation according to [any one of] claim[s] 1 [to 3], characterized in that the organic acid salt is an acetic acid salt.

Please add the following new claims:

7. The adhesive preparation according to claim 2 comprising the organic acid salt of 0.01-15% by weight.

8. The adhesive preparation according to claim 2 comprising the base drug salt of 0.1-20% by weight.

9. The adhesive preparation according to claim 2, characterized in that the organic acid salt is an acetic acid salt.

10. The adhesive preparation according to claim 9, characterized in that the organic acid salt is sodium acetate.

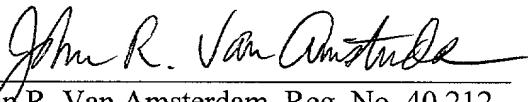
11. The adhesive preparation according to claim 3, characterized in that the organic acid salt is an acetic acid salt.

12. The adhesive preparation according to claim 11, characterized in that the organic acid salt is sodium acetate.

Remarks

Please enter this amendment prior to calculation of the fees. Original PCT claims 3, 4 and 5 were amended to remove multiple dependencies, and claims 7-12 were added accordingly to claim the subject matter of the original claims. New claim 7 corresponds to original claim 3. New claim 8 corresponds to original claim 4. New claims 9 and 11 correspond to original claim 5. New claims 10 and 12 correspond to original claim 6. No new matter has been added.

Respectfully submitted,

  
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Docket No.: K0448/7003  
Date: October 13, 2000  
**X10/17/00**

3/PK

## Specification

Title of the Invention: Adhesive preparations**TECHNICAL FIELD**

5 The invention relates to a percutaneous absorption preparation which contains a salt of a base drug and is excellent in skin permeability of the drug.

**BACKGROUND ART**

As administration methods for drugs, various methods such as oral administration, rectal administration, intracutaneous administration and intravenous administration are known, and among them oral administration is widely been adopted. However, in case of oral administration, there are drawbacks that a drug is susceptible to the first-pass effect in the liver after absorption of the drug and an unnecessarily high blood concentration is recognized for a while after the administration. Also, in oral administration many side effects such as gastrointestinal tract disorder, vomiting feeling and loss of appetite have been reported. Further, in recent aged society patients with reduced swallowing power increase, and preparations easy for administration clinically are desired.

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Therefore, by dissolving these drawbacks of oral administration with the aim of percutaneous preparations for patients to take more easily with safety and persistence, development of such percutaneous administration preparations has actively been carried out, and the products are commercially

available.

However, percutaneous absorbance of drugs in said percutaneous administration preparations is still insufficient in many cases, and the development of percutaneous administration 5 preparations is difficult due to low percutaneous absorbance of most drugs, so it can hardly be said that the objects have sufficiently been attained. Namely, since normal skin has barrier function to prevent penetration of foreign substances, sufficient percutaneous absorption of a compounded pharmaceutically active ingredient is hardly attained in many 10 cases.

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Therefore, devices to increase percutaneous absorbance of a drug through a stratum corneum of skin has been needed, and compounding so-called percutaneous absorption promotors to a base has generally been tried. For example, as an absorption promoter combined with a lower alkyl amide, dimethylacetamide and ethyl alcohol, isopropyl alcohol, isopropyl palmitate or the like (US, 3,472,931, A), combining 2-pyrrolidone and an appropriate oil, and a straight chain fatty acid and alcohol ester ((US, 4,017,641, A), and combining lower alcohol and C<sub>7</sub>-C<sub>20</sub> alcohol, C<sub>5</sub>-C<sub>30</sub> fatty acid hydrocarbon, alcohol ester of C<sub>19</sub>-C<sub>26</sub> fatty acid carboxylic acid, C<sub>10</sub>-C<sub>24</sub> mono- or di-ether, C<sub>11</sub>-C<sub>15</sub> ketone and water (JP, 61-249934, A) and the like have been proposed. However, it can hardly be said that these conventional absorption promotors and absorption promoting compositions are yet sufficiently safe for skin.

Further, as a percutaneous absorption preparation, methods of combining a drug and an organic acid have been reported. For example, a tape preparation combining betamethazone valerate and an organic acid to a natural rubber type adhesive (JP, 56-61312, 5 A), a tape preparation combining a non-steroidal anti-inflammatory agent and an organic acid to an acrylic type adhesive agent (JP, 62-126119, A (US 4,740,374, A)), and a pap type preparation combining methyl salicylate as a pharmaceutically effective ingredient, an emulsifier, an organic acid, a plasticizer, a tackifying resin and water to a styrene-isoprene-styrene block copolymer (JP, 63-159315, A) and the like have already been proposed. However, the aim of using these organic acids in the above publications is to improve stability and solubility, and was a pH-adjusting agent, and because these drugs are acidic or neutral, they are not the preparations in which skin permeability of a physiologically active substance is improved via an ion-pair formation constructed by an organic acid of the present invention.

Further, a method to improve skin permeability of a basic physiologically active substance has been tried. For example, a tape preparation combining citric acid and isoproterenol hydrochloride to an acrylic type adhesive (JP, 63-79820, A), a tape preparation combining an organic acid and vincristine to an acrylic type adhesive (JP, 5-25039, A) and the like have been reported, though these have a problem of irritancy at the time of dissection, and that the released amount of the drugs do not

give a sufficient effect for therapy.

The invention was made to dissolve the problems of the prior art described above, and makes it an object to provide a matrix type adhesive preparation. In WO, 96/16642, A, technology of an adhesive preparation in which an organic acid salt is contained in a salt type base drug is disclosed, though the effect of the particle size of the contained organic salt is not demonstrated.

#### **DISCLOSURE OF THE INVENTION**

During extensive researches to solve these problems the inventors found out that comprising an organic acid salt of a particular particle size in adhesive preparations containing a base drug as a salt form improves solubility of the drug to skin via an ion-pair formation, and that it significantly improves skin permeability of the drug by enhancing partition coefficient to skin, and thus accomplished the invention. Specifically, in case of the mean diameter of a base drug and an organic acid salt contained was 100 $\mu$ m or less (this particle size indicates volume average particle size when measured by the use of a particle fineness analyzer) the effect was observed. Particularly, it was revealed that in a fat-soluble base, though the solubility of a drug and an organic acid salt was so bad they remain as powder in the preparation, percutaneous absorbance of the drug was greatly affected by the size of the particle diameter of the organic acid salt. In particular, as an organic acid salt, the effect of sodium acetate is high, and in this case the average particle size of 0.1-10 $\mu$ m shows extremely excellent percutaneous

drug-absorbance promoting effect.

Accordingly, the invention relates to an adhesive preparation comprising a base drug salt, and an organic acid salt in which the mean diameter is 0.1-100 $\mu$ m.

5 The invention also relates to the above adhesive preparation wherein the mean diameter of the organic acid salt is 0.1-10 $\mu$ m.

Further, the invention relates to the above adhesive preparation comprising the organic acid salt of 0.01-15% by weight.

10 The invention also relates to the above adhesive preparation comprising the base drug of 0. 1-20% by weight.

Furthermore, the invention relates to the above adhesive preparation characterized in that the organic acid is acetic acid.

15 And the invention relates to the above adhesive preparation characterized in that the organic acid is sodium acetate.

Further, adhesive preparations of the invention provide excellent skin permeability, skin irritancy and content stability of a drug and physical stability of a base.

20 The adhesive preparations of the invention are also preferably matrix type preparations.

#### **Brief Description of Drawing**

Fig. 1

Graph showing the results of skin permeability of Examples 25 1-3 and Comparative example 1.

Fig. 2

Graph showing the results of skin permeability of Examples 6-8 and Comparative examples 4-5.

Fig. 3

Graph showing the results of skin permeability of Examples 5 11-13 and Comparative examples 8-9.

In any drug, powders with a smaller particle size gave more excellent skin permeability to the drug.

#### **Embodiment of the Invention**

As the embodiment of the invention, the composition and the form in the adhesive layer of the adhesive preparations related to the invention is explained.

Illustrative of the organic acid salts used in the adhesive layer of the adhesive preparations according to the invention are respective water-soluble inorganic salts of aliphatic (mono, di, tri)carboxylic acids (e.g., acetic acid, propionic acid, isobutylic acid, caproic acid, lactic acid, maleic acid, pyruvic acid, oxalic acid, succinic acid, tartaric acid, etc.) , aromatic carboxylic acids (e.g., phthalic acid, salicylic acid, benzoic acid, acetyl salicylic acid, etc.), alkyl sulfonic acids (e.g., 20 ethane sulfonic acid, propyl sulfonic acid, butane sulfonic acid, polyoxyethylene alkyl ether sulfonic acid, etc.), alkyl sulfonic acids (e.g., N-2-hydroxyethyl piperidine-N'-2-ethane sulfonic acid (hereafter abbreviated as HEPES) etc.) and cholic acid derivatives (e.g., dehydro cholic acid, etc.), and in particular 25 sodium acetate is preferable. Further, these organic acid salts may be anhydrous or hydrated, though in case used in a hydrophobic

adhesive layer, an anhydride is preferred.

Considering a sufficient permeable amount and irritancy to the skin for an adhesive preparation, these organic salts can be blended in an amount of preferably 0.01-15% by weight, more preferably 0.1-10% by weight, and most preferably 0.1-5% by weight based on the total weight of the composition in the adhesive preparation.

Also, in the case of a commercially available powder in which the average particle size of an organic acid salt is not less than about 100 $\mu\text{m}$  (in the case of sodium acetate, generally the average particle size of commercially available one is not less than about 500 $\mu\text{m}$ ), it is ground in a preparation step to not more than 100 $\mu\text{m}$  to obtain an excellent percutaneous drug absorbance, and the average particle size is made preferably 0.1-100 $\mu\text{m}$ , more preferably 0.1-50 $\mu\text{m}$ , and most preferably 0.1-10 $\mu\text{m}$ . Namely, it is considered that an ion-pair formation is more sufficiently promoted as the particle size of powders becomes smaller. As a method to grind an organic acid salt, powders which are dry ground beforehand may be used, or not yet ground one is added to a solution containing other base ingredients and may be wet ground under stirring. For example, as a grinder mill of dry process, a supersonic jet grinder mill, Jet Mill, (manufactured by Nippon Pneumatic MFG Co., Ltd.) and the like, or as a grinder mill of wet process, an ultra-micro grinder mill, Micros, (manufactured by Nara Machinery Co., Ltd.) and the like can be used.

Further, as a drug used in the adhesive layer of the adhesive

preparations of the invention, an inorganic salt forming an ion-pair with an organic acid or its salt, or any base drug salt formed by an organic acid is not limited particularly by their types; examples include hypnotic-sedative agents (fluazepam hydrochloride, rilmazafone hydrochloride, etc.), anti-  
5 inflammatory agents (butorphanol tartarate, persoxal citrate, etc.), excitation-analeptic agents (methanephedrine hydrochloride, methylphenidate hydrochloride, etc.), psychotropic agents (chlorpromazine hydrochloride, imipramine hydrochloride, etc.), local anesthetic agents (lidocain hydrochloride, procaine hydrochloride), agents for urinary organs (oxybutynin hydrochloride, etc.), skeletal muscle relaxants (tizanidine hydrochloride, eperisone hydrochloride, pridinol mesilate, etc.), autonomic agents (carpronium chloride, neostigmine bromide, etc.), anti-Parkinson's disease agents (trihexyphenidyl hydrochloride, amantadine hydrochloride, etc.),  
10 antihistaminic agents (clemastine fumarate, diphenhydramine tannate, etc.), bronchodilator agents (tulobuterol hydrochloride, procaterol hydrochloride, etc.), cardiotonic agents (isoprenaline hydrochloride, dopamine hydrochloride, etc.), coronary dilators (diltiazem hydrochloride, verapamil hydrochloride, etc.), peripheral vasodilators (nicametate citrate, tolazoline hydrochloride, etc.), cardiovascular agents (flunarizine hydrochloride, nicardipine hydrochloride, etc.),  
15 antiarrhythmic agents (propranolol hydrochloride, alprenolol hydrochloride, etc.), antiallergic agents (ketotifen fumarate,  
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azelastine hydrochloride, etc.), anti-dizziness agents (betahistine mesilate, difenidol hydrochloride, etc.), serotonin receptor antagonistic antiemetics, narcotic analgesic agents (morphine sulfate, fentanyl citrate, etc.).

5        Further, these drugs may be used alone or in combination of two or more of them, and any form of drug, an inorganic salt or an organic salt, are naturally included. Also, considering a sufficient permeable amount as adhesive preparations and irritancy to the skin such as rubor, drugs can be blended in an amount preferably of 0.01-15% by weight, and more preferably 0.1-20% by weight based on the total weight of the composition in the adhesive layer.

10        *U.S. Pat. No. 4,737,450*  
15        *U.S. Pat. No. 4,737,451*

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Any absorption promotor may be contained in the adhesive layer of the adhesive preparations of the invention, and as an absorption promotor, any compound in which absorption promoting effect is shown may be used. Examples include C<sub>6</sub>-C<sub>20</sub> fatty acids, fatty alcohols, fatty acid esters or ethers, aromatic organic acids, aromatic alcohols, aromatic fatty acid esters or ethers (these may be saturated or unsaturated, and cyclic, straight or branched), furthermore lactic acid esters, acetic acid esters, monoterpene compounds, sesquiterpene compounds, Azone, Azone derivatives, glycerol fatty acid esters, sorbitan fatty acid esters (Span type), polysorbates (Tween type), polyethylene glycol fatty acid esters, polyoxyethylene hardened castor oils (HCO type), sucrose fatty acid esters and the like.

Specifically, caprylic acid, capric acid, lauric acid,

myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, lauryl alcohol, myristyl alcohol, oleyl alcohol, cetyl alcohol, methyl laurate, isopropyl myristate, myristyl myristate, octyldecyl myristate, cetyl palmitate, 5 salicylic acid, methyl salicylate, glycol salicylate, cinnamic acid, methyl cinnamate, cresol, cetyl lactate, ethyl acetate, propyl acetate, geraniol, thymol, eugenol, terpineol, 1-menthol, borneol, d-limonene, isoeugenol, isoborneol, nerol, dl-camphor, glycerol monolaurate, glycerol monooleate, sorbitan monolaurate, sucrose monolaurate, polysorbate 20, propylene glycol, 10 polyethylene glycol monolaurate, polyethylene glycol monostearate, HCO-60, and 1-[2-(decylthio)ethyl]azacyclopentan-2-one (hereafter abbreviated as pyrothiodescane) are preferred, and lauryl alcohol, 1-menthol, propylene glycol and pyrothiodescane are particularly preferred.

Considering a sufficient permeable amount as adhesive preparations and irritancy to the skin such as rubor and edema, such absorption promoters can be blended in an amount preferably of 0.01-20% by weight, more preferably 0.05-10% by weight and 20 most preferably 0.1-5% by weight based on the total weight of the composition in the adhesive preparations.

As a fat soluble hydrophobic polymer used in the adhesive layer of the adhesive preparations of the invention, examples include styrene-isoprene-styrene block copolymer (hereinafter abbreviated as SIS), isoprene rubber, polyisobutylene 25 (hereinafter abbreviated as PIB), styrene-butadiene-styrene

block copolymer (hereinafter abbreviated as SBS), styrene-butadiene rubber (hereinafter abbreviated as SBR), acrylic type polymer (copolymer of at least two types from 2-ethylhexyl acrylate, vinyl acetate, methacrylate, methoxyethyl acrylate and acrylic acid). In particular, SIS, PIB or blends thereof, and acrylic type polymer are preferred.

Considering formation of the adhesive layer and sufficient permeability, the blended amount of such hydrophobic polymers based on the total weight of the composition in the adhesive layer can be 10-60% by weight, preferably 15-50% by weight, more preferably 18-40% by weight in SIS, PIB or the like. Similarly, it can be 10-98% by weight, preferably 20-98% by weight, more preferably 30-98% by weight in acrylic type polymer.

As a tackifying resin used in the adhesive layer of the adhesive preparations of the invention, examples include rosin derivatives (e.g., rosin, glycerol esters of rosin, hydorogenated rosin, glycerol esters of hydorogenated rosin, pentaerythritol esters of rosin, etc.), alicyclic saturated hydrocarbon resins, aliphatic hydrocarbon resins, terpene resins, maleic acid resins and the like. In particular, glycerol esters of hydorogenated rosin, alicyclic saturated hydrocarbon resins, aliphatic hydrocarbon resins and terpene resins are preferred.

Considering sufficient adhesive strength as the adhesive preparations and irritancy to the skin at the time of dissection, the compounded amount of such tackifying resins based on the total weight of the composition in the adhesive layer can be 10-70%

by weight, preferably 15-60% by weight, and more preferably 20-50%.

As a plasticizer used in the adhesive layer of the adhesive preparations of the invention, examples include petroleum oils (e.g., paraffin type process oil, naphthalene type process oil, aromatic type process oil, etc.), squalene, vegetable oils (olive oil, camellia oil, castor oil, tall oil, peanut oil), dibasic acid esters (e.g., dibutyl phthalate, dioctyl phthalate, etc.), liquid rubber (e.g., polybutene, liquid isoprene rubber), diethylene glycol, polyethylene glycol, glycol salicylate, propylene glycol, dipropylene glycol, crotamiton and the like. In particular, liquid paraffin, liquid polybutene, glycol salicylate and crotamiton are preferred.

Considering sufficient permeability and the maintenance of sufficient agglutinative strength as adhesive preparations, the blended amount of such a tackifying resin based on the total weight of the composition in the adhesive layer can be 10-70% by weight, preferably 15-60% by weight, and more preferably 20-50%.

Also, as required, antioxidants, fillers, cross-linking agents, preservatives or UV absorbers can be used. As antioxidants, tocopherol and its ester derivatives, ascorbic acid, ascorbic acid-stearic acid ester, nordihydroguaiaretic acid, dibutyl hydroxy toluene (BHT), butyl hydroxy anisole and the like are desirable. As fillers, calcium carbonate, magnesium carbonate, silicate (e.g., aluminum silicate, magnesium silicate, etc.), silicic acid, barium sulfate, calcium sulfate, calcium

zincate, zinc oxide, titanic oxide and the like are desirable.

As cross-linking agents, thermosetting resins such as amino resins, phenol resins, epoxy resins, alkyd resins, unsaturated polyesters, etc., isocyanate compounds, block isocyanate

5 compounds, organic type cross-linking agents, and inorganic type cross-linking agents such as metals or metal compounds, are desirable. As preservatives, ethyl p-oxybenzoate, propyl p-oxybenzoate, butyl p-oxybenzoate and the like are desirable. As UV absorbers, p-amino benzoic acid derivatives, anthranilic acid derivatives, salicylic acid derivatives, coumarin derivatives, amino acid type compounds, imidazoline derivatives, pyrimidine derivatives, dioxane derivatives and the like are desirable.

10 Such antioxidants, fillers, cross-linking agents, preservatives or UV absorbers can be blended in total preferably in an amount of not more than 10% by weight, more preferably not more than 5% by weight and most preferably not more than 2% by weight based on the total weight of the composition in the adhesive 15 layer of the adhesive preparations.

20 The adhesive layer having such a composition can be prepared by any method. For example, a base composition containing a drug is heat-melted, coated on removable paper or a backing, followed by affixing each to the backing or the removable paper to give the present preparations. Also, base ingredients containing a drug are dissolved in solvent such as toluene, hexane or ethyl acetate, spreaded on removable paper or a backing, dried to remove 25 solvent, followed by affixing to the backing or the removable

paper to give the present preparations.

Further, the adhesive preparations of the invention may take any other structures and materials for each constituent, if the adhesive layer has the above composition containing the organic acid salt and the drug.

For example, in addition to the above adhesive layer the adhesive preparations of the invention can comprise of a backing layer to support it and a removable paper layer set on the adhesive layer.

As to the backing layer, an elastic or a non-elastic backing can be used. For example, it can be selected from fabric, polyurethane, polyester, polyvinyl acetate, polyvinylidene chloride, polyethylene, polyethylene terephthalate, aluminum sheet and the like, or composite materials thereof.

#### **Example**

In the following, the invention is explained in more detail by the examples. The invention, however, is not limited to these examples, and various changes may be made without departing from the spirit of the invention. Further, in the examples, all "%"s mean % by weight.

#### **Example 1**

Styrene-isoprene-styrene block copolymer (SIS)	24.0%
Alicyclic saturated hydrocarbon (Arkon P-100)	29.5%
Liquid paraffin (Crystol 352)	41.0%
Pyrothiodecane	2.0%
Sodium acetate	1.5%

Ketotifen fumarate	1.5%
<u>Butyl hydroxy toluene [BHT (Yoshinox)]</u>	0.5%
Total amount	100.0%

Sodium acetate (average particle size 7  $\mu\text{m}$ ) ground by Jet Mill beforehand was used, and the polymer contained was heat-melted. The components were coated on removable paper, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

### Example 2

Sodium acetate (average particle size 43  $\mu\text{m}$ ) ground using a mortar beforehand was used, and the other ingredients and the preparation steps were the same as those of Example 1.

### Example 3

Sodium acetate (average particle size 91  $\mu\text{m}$ ) ground using a mortar beforehand was used, and the other ingredients and the preparation steps were the same as those of Example 1.

Example 4

	SIS	22.5%
	Alicyclic saturated hydrocarbon (Arkon P-85)	27.5%
20	Liquid paraffin	32.0%
	Lauryl alcohol	5.0%
	Sodium acetate	5.0%
	Lidocain hydrochloride	7.5%
	<u>BHT</u>	0.5%
25	Total amount	100.0%

Sodium acetate (average particle size 43  $\mu\text{m}$ ) ground using

mortar beforehand was used, and the polymer contained was heat-melted. The components were coated on removable paper, followed by affixing the removal paper to the backing to give the matrix adhesive preparation of the invention.

5 Example 5

SIS	15.5%
Polyisobutylene (PIB)	6.5%
Alicyclic saturated hydrocarbon (Arcon P-100)	33.0%
Liquid paraffin	31.5%
10 Crotamiton	5.0%
Sodium acetate	3.0%
Oxybutynin hydrochloride	5.0%
<u>BHT</u>	<u>0.5%</u>
Total amount	100.0%

15 Sodium acetate (average particle size 43  $\mu\text{m}$ ) ground using a mortar beforehand was used, and the polymer contained was heat-melted. The components were coated on removable paper, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

20 Example 6

SIS	26.0%
Hydrogenated rosin ester	35.0%
Liquid paraffin	28.6%
Crotamiton	5.0%
25 Pyrothiodescane	3.0%
Sodium acetate	0.4%

Tizanidine hydrochloride	1.5%
<u>BHT</u>	0.5%
Total amount	100.0%

5 All the compositions including sodium acetate (average particle size 7  $\mu\text{m}$ ) ground by Jet Mill beforehand were dissolved in toluene, coated on removable paper, dried to remove solvent, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

Example 7

10 Sodium acetate (average particle size 43  $\mu\text{m}$ ) ground using a mortar beforehand was used, and the other ingredients and the preparation steps were the same as those of Example 6.

Example 8

15 Sodium acetate (average particle size 91  $\mu\text{m}$ ) ground using a mortar beforehand was used, and the other ingredients and the preparation steps were the same as those of Example 6.

Example 9

PIB	28.5%
Rosin ester	29.5%
20 Liquid paraffin	33.5%
1-Menthol	3.0%
Sodium acetate	2.0%
Pridinol mesylate	3.0%
<u>BHT</u>	0.5%
25 Total amount	100.0%

All the compositions including sodium acetate (average

particle size 7  $\mu\text{m}$ ) ground by Jet Mill beforehand was dissolved in toluene, coated on removable paper, dried to remove solvent, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

5 Example 10

SIS	20.5%
PIB	5.5%
Terpene resin (YS resin Px1000)	21.0%
Liquid paraffin	44.0%
Propylene glycol	2.5%
Sodium acetate	3.0%
Tulobuterol hydrochloride	3.0%
<u>BHT</u>	<u>0.5%</u>
Total amount	100.0%

10 All the compositions including sodium acetate (average particle size 91 $\mu\text{m}$ ) ground using a mortar beforehand were dissolved in toluene, coated on removable paper, dried to remove solvent, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

20 Example 11

SIS	24.0%
Alicyclic saturated hydrocarbon resin (Arcon P-100)	30.0%
Liquid paraffin	38.0%
pyrothiodescane	3.0%
Sodium acetate	1.5%
Fentanyl citrate	3.0%

BHT

0.5%

Total amount 100.0%

Among the above ingredients, all the powder ingredients (sodium acetate, fentanyl citrate) were contained in liquid paraffin, ground by Micros to make the mean diameter 10  $\mu\text{m}$  or smaller. This and the other ingredients were dissolved in toluene, coated on removable paper, dried to remove solvent, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

**10** Example 12

Sodium acetate (average particle size 43  $\mu\text{m}$ ) ground using a mortar beforehand was used, and the other ingredients were the same as those of Example 11, whereby the preparation was formulated using a stirrer which has no grinder function.

**15** Example 13

Sodium acetate (average particle size 91  $\mu\text{m}$ ) ground using a mortar beforehand was used, and the other ingredients were same as those of Example 11, whereby the preparation was formulated using a stirrer which has no grinder function.

**20** Example 14

SIS	21.0%
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PIB	9.5%
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Aliphatic type hydrocarbon resin (Quintone B170)	25.0%
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Polybutene	5.5%
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25 Liquid paraffin	28.5%
--------------------	-------

Propylene glycol	3.0%
------------------	------

Sodium acetate	2.0%
Propranolol hydrochloride	5.0%
<u>BHT</u>	<u>0.5%</u>
Total amount	100.0%

5 Among the above ingredients, all the powder ingredients (sodium acetate, propranolol hydrochloride) were contained in liquid paraffin, ground by Micros to make the mean diameter 50  $\mu\text{m}$  or smaller. This and the other ingredients were dissolved in toluene, coated on removable paper, dried to remove solvent, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

10 Example 15

SIS	18.0%
PIB	6.0%
Alicyclic saturated hydrocarbon resin (Arkon P-100)	31.5%
Liquid paraffin	30.5%
Lauryl alcohol	5.0%
Sodium acetate	5.0%
Azelastine hydrochloride	3.5%
<u>BHT</u>	<u>0.5%</u>
Total amount	100.0%

15 Among the above ingredients, all the powder ingredients (sodium acetate, azelastine hydrochloride) were contained in liquid paraffin, ground by Micros to make the mean diameter 100  $\mu\text{m}$  or smaller. This and the other ingredients were dissolved in toluene, coated on removable paper, dried to remove solvent,

followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

Example 16

5 Acrylic polymer (Nissetsu PE-300:  
Nippon Carbide Industries Co., INC.) 92.0%

Cross-linking agent (Nissetsu CK-100:  
Nippon Carbide Industries Co., INC.) 0.5%

1-Menthol 3.0%

Sodium acetate 1.5%

10 Fentanyl citrate 3.0%

Total amount 100.0%

Among the above ingredients, 1-menthol, fentanyl citrate and sodium acetate (average particle size 7  $\mu\text{m}$ ) ground by Jet Mill beforehand were added to ethanol, dissolved under stirring at room temperature. The mixture was then added with an ethyl acetate solution of the acrylic polymer and with the cross-linking agent, stirred, coated on removable paper, dried to remove solvent, followed by a heat cross-linking and by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

**COMPARATIVE EXAMPLE**

Comparative example 1

Sodium acetate (average particle size 535  $\mu\text{m}$ ) not yet ground was used, and the other ingredients and the preparation steps 25 were the same as those of Example 1.

Comparative example 2

Sodium acetate (average particle size 535  $\mu\text{m}$ ) not yet ground

was used, and the other ingredients and the preparation steps were the same as those of Example 4.

Comparative example 3

Sodium acetate (average particle size 535  $\mu\text{m}$ ) not yet ground was used, and the other ingredients and the preparation steps were the same as those of Example 5.

Comparative example 4

Sodium acetate (average particle size 200  $\mu\text{m}$ ) ground using a mortar beforehand was used, and the other ingredients and the preparation steps were the same as those of Example 6.

Comparative example 5

Sodium acetate (average particle size 535  $\mu\text{m}$ ) not yet ground was used, and the other ingredients and the preparation steps were the same as those of Example 6.

Comparative example 6

Sodium acetate (average particle size 535  $\mu\text{m}$ ) not yet ground was used, and the other ingredients and the preparation steps were the same as those of Example 9.

Comparative example 7

Sodium acetate (average particle size 535  $\mu\text{m}$ ) not yet ground was used, and the other ingredients and the preparation steps were the same as those of Example 10.

Comparative example 8

Sodium acetate (average particle size 139  $\mu\text{m}$ ) ground using a mortar beforehand was used, and the other ingredients were same as those of Example 11, whereby the preparation was formulated

using a stirrer which has no grinder function.

Comparative example 9

Sodium acetate (average particle size 535  $\mu\text{m}$ ) not yet ground was used, and the other ingredients were the same as those of Example 11, whereby the preparation was formulated using a stirrer which has no grinder function.

Comparative example 10

Sodium acetate (average particle size 535  $\mu\text{m}$ ) not yet ground was used, and the other ingredients were the same as those of Example 14, whereby the preparation was formulated out using a stirrer which has no grinder function.

Comparative example 11

Sodium acetate (average particle size 535  $\mu\text{m}$ ) not yet ground was used, and the other ingredients were the same as those of Example 15, whereby the preparation was formulated using a stirrer which has no grinder function.

Comparative example 12

Sodium acetate (average particle size 535  $\mu\text{m}$ ) not yet ground was used, and the other ingredients and the preparation steps were the same as those of Example 16.

(Skin permeability test on hairless mice)

Dorsal skin of a hairless mouse was stripped, and the dermal side was placed to the receptor layer side and installed in a flow-through cell ( $5 \text{ cm}^2$ ) around whose periphery warm water at 37 °C was circulated. Each of the adhesive preparations obtained in the examples 1-3, 6-8 and 11-13 as well as the comparative

examples 1, 4, 5, 8 and 9 was coated on the stratum corneum side, and sampling was carried out every one hour (or 2 hours) for 12 hours (or 18 hours, 24 hours) at the rate of 5 ml/hour using the physiological saline in the receptor layer. As to the receiver 5 solutions obtained at every hour, the flow amounts were accurately measured, and the drug concentrations were measured by high-performance liquid chromatography, followed by calculation of the permeation rate per hour to determine the skin permeability rate according to the following equation.

10 Skin permeability rate ( $\mu\text{g}/\text{cm}^2/\text{hr}$ ) =  
{sample concentration ( $\mu\text{g}/\text{ml}$ )  $\times$  flow amount (ml)}/{applied area of the preparation ( $\text{cm}^2$ )}

#### 15 **Industrial Applicability**

According to the adhesive preparations of the invention, 15 drugs can be efficiently absorbed into circulating blood via skin. Also, side effects of the gastrointestinal system observed in case of oral administration, and side effects in the central nervous system which can occur due to a rapid increase of the blood concentration can be avoided. Further, they are extremely 20 low in irritancy to the skin. Therefore, these are very effective as external preparations aiming at percutaneous application.

### Claim

1. An adhesive preparation comprising a base drug salt and an organic acid salt in the form of powder having a mean diameter of 0.1-100  $\mu\text{m}$ .
2. The adhesive preparation according to claim 1, wherein the mean diameter of the organic acid salt is 0.1-10  $\mu\text{m}$ .
3. The adhesive preparation according to claim 1 or 2 comprising the organic acid salt of 0.01-15% by weight.
4. The adhesive preparation according to claim 1 or 2 comprising the base drug salt of 0.1-20% by weight.
5. The adhesive preparation according to any one of claims 1 to 3, characterized in that the organic acid salt is an acetic acid salt.
6. The adhesive preparation according to claim 5, characterized in that the organic acid salt is sodium acetate.

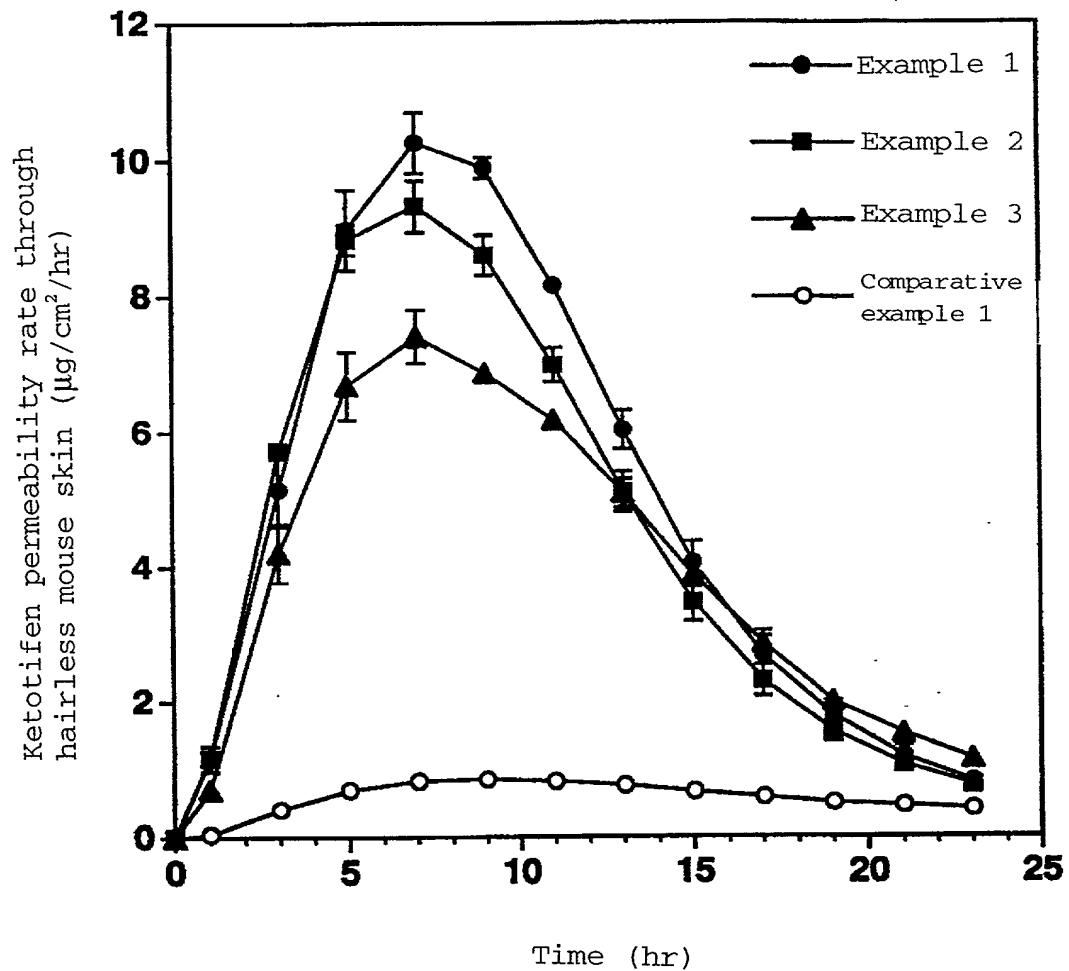
10  
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20

## **Abstract**

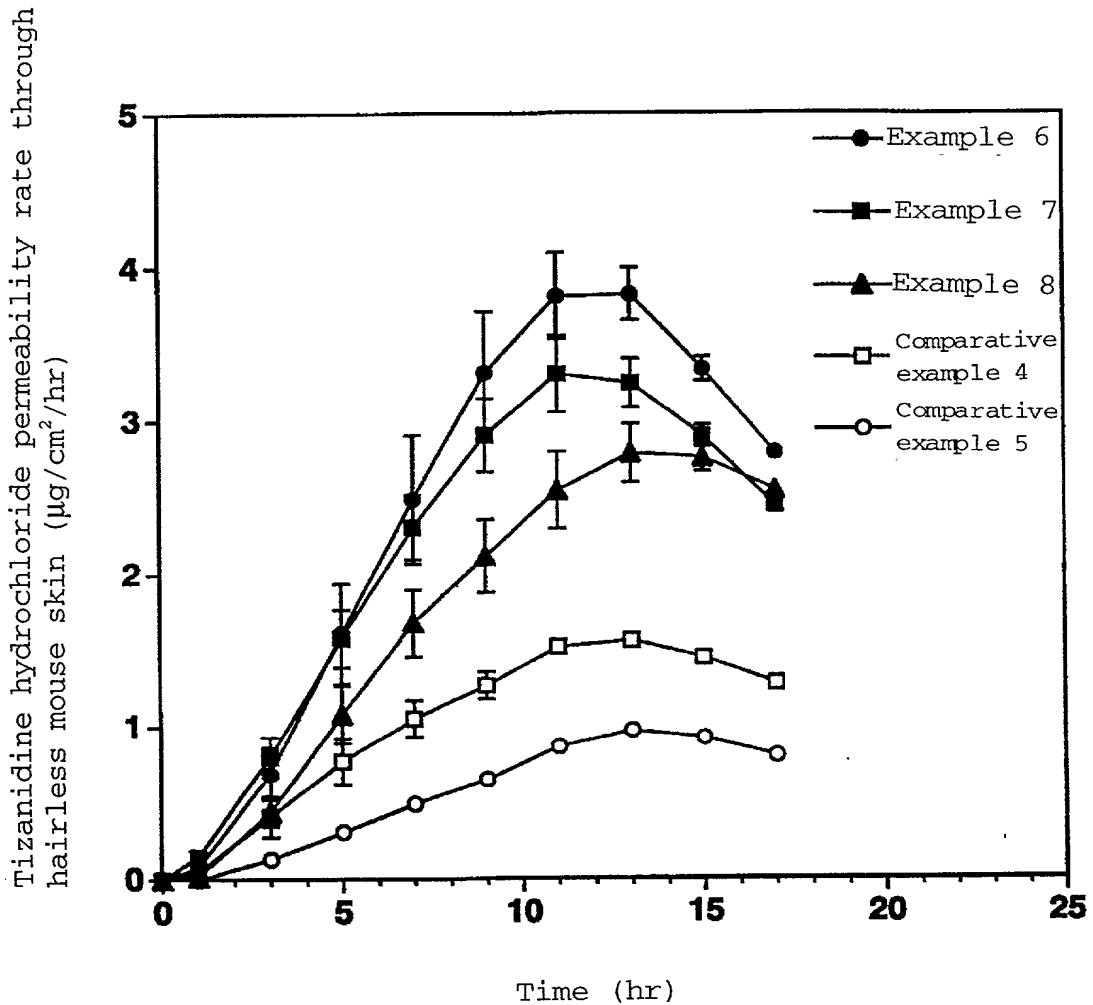
Adhesive preparations with improved percutaneous absorption of physiologically active substances, in particular, matrix adhesive preparations containing a base drug salt and an organic acid salt having a mean diameter of from 0.1 to 100  $\mu\text{m}$  are provided.

Fig. 1



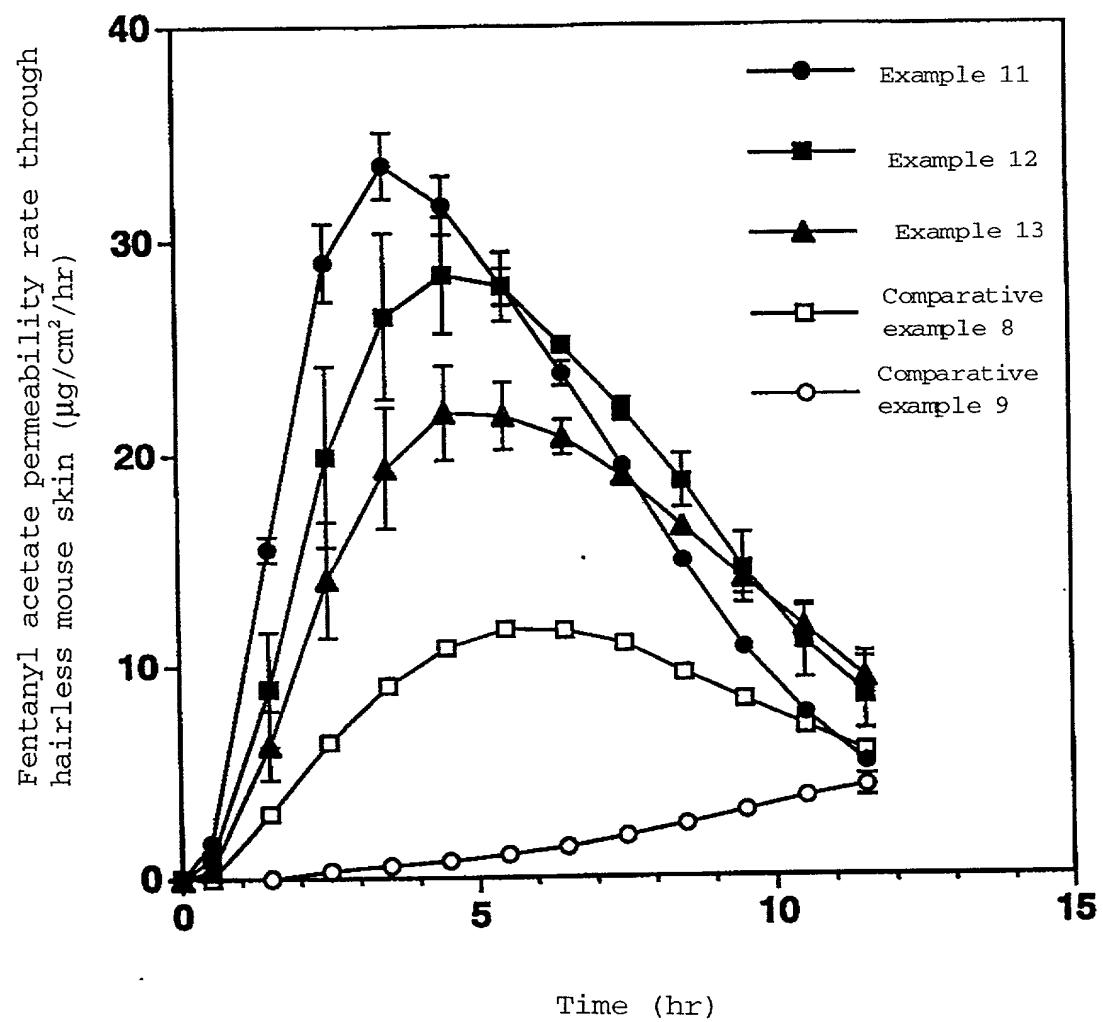
Effects of grinding powder ingredients on permeability of ketotifen formulate through hairless mouse skin

Fig. 2



Effects of grinding powder ingredients on permeability of tizanidine hydrochloride through hairless mouse skin

Fig. 3



Effects of mean diameter on permeability of fentanyl citrate through hairless mouse skin

Attorney Docket No. K0448/

**DECLARATION FOR PATENT APPLICATION**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**ADHESIVE PREPARATIONS**

the specification of which is attached hereto unless the following is checked:

was filed on April 8, 1999, as PCT International Application No. PCT/JP99/01868, bearing attorney docket No. K0448/.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or section 365(a) of any PCT International application designating at least one country other than the United States listed below and have also identified below any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed:

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		Priority Claimed	
<u>10-122758</u> (Number)	<u>Japan</u> (Country-if PCT, so indicate)	<u>17/04/98</u> (DD/MM/YY Filed)	<input checked="" type="checkbox"/> [ ] YES NO
_____ (Number)	_____ (Country-if PCT, so indicate)	_____ (DD/MM/YY Filed)	[ ] [ ] YES NO
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(Application Number)	(filing date)
_____ (Application Number)	_____ (filing date)

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(Application No.)	(filing date)	(status-patented, pending, abandoned)
(Application No.)	(filing date)	(status-patented, pending, abandoned)

PCT International Applications designating the United States:

(PCT Appl. No.)	(U.S. Ser. No.)	(PCT filing date)	(status-patented, pending, abandoned)

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or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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